PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification [4]: A61L 9/04, A61K 31/70, A61M 11/00, B05B 7/30, A61M 37/00

A1

(11) International Publication Number: WO 86/ 05987

(43) International Publication Date: 23 October 1986 (23.10.86)

(21) International Application Number: PCT/US86/00665

(22) International Filing Date: 2 April 1986 (02.04.86)

(31) Priority Application Number: 723,859

(32) Priority Date: 16 April 1985 (16.04.85)

(33) Priority Country: US

(71) Applicant: NASTECH PHARMACEUTICAL COMPANY, INC. [US/US]; 800 Veterans Memorial Highway, Hauppauge, NY 11788 (US).

(72) Inventor: WENIG, Jeffrey ; 9 Dickens Avenue, Dix Hills, NY 11746 (US).

(74) Agents: BURKE, Henry, T. et al.; Wyatt, Gerber, Shoup, Scobey & Badie, 261 Madison Avenue, New York, NY 10016 (US).

(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.

(54) Title: AEROSOL COMPOSITIONS FOR NASAL DELIVERY OF VITAMIN B_{12}

(57) Abstract

Aerosol compositions useful for the nasal administration of a vitamin B_{12} and methods of administration.

8 April 1985

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BG	Bulgaria
BR	Brazil
CF	Central African Republic
CG	Congo
CH	Switzerland
CM	Cameroon
DE	Germany, Federal Republic of
DK	Denmark
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
HU	Hungary
IT	Italy
JP	Japan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
MC	Monaco
MG	Madagascar
ML	Mali
MR	Mauritania
MW	Malawi
NL	Netherlands
NO	Norway
RO	Romania
SD	Sudan
SE	Sweden
SN	Senegal
SU	Soviet Union
TD	Chad
TG	Togo
US	United States of America

AEROSOL COMPOSITIONS FOR NASAL DELIVERY OF VITAMIN B12

BACKGROUND OF THE INVENTION

This invention is concerned with aerosol compositions for nasal administration of a vitamin B_{12} to a human suffering a vitamin B_{12} deficiency. It is concerned also with methods of administering such compositions.

Cyanocobalamin is a vitamin B_{12}, and is one of the B_{12} class of vitamins which includes vitamin B_{12a} (hydroxocobalamin), vitamin B_{12b} (aquacobalamin), vitamin B_{12b} (nitrilocobalamin), coenzyme B_{12} (5'-deoxyadenosine cobalamine) amd methyl B_{12} (methyl cobalamine). Cyanocobalamin is the principal member of the class, and the most widely employed in medicine. This invention will be described as it relates to cyanocobalamin, but those skilled in the art will recognize that the invention is applicable to the class.

Vitamin B_{12} is an essential compound for normal growth, hematopoiesis, production of all epithelial cells and maintenance of myelin throughout the nervous system. It was first isolated from liver concentrate by Rickes and his coworkers in 1948 and structurally elucidaated by Hodgkin and her coworkers in the late 1950's. It is currently commercially available as a tablet and as an injectable.

Therapeutically, vitamin B_{12} is employed in the treatment of a variety of B_{12} deficiency afflictions, principally anemias such as pernicious and diphyllobothrium latum. Although the minimum

daily requirement of vitamin B_{12} is approximately -.1ug, the generally prescribed initial therapeutic dose is 100 to 1000ug given intramuscularly. Maintenance therapy with vitamin B_{12} is usually 100ug intramuscularly, monthly and must be continued for life.

Since pernicious anemia is often a disease of later years when many sufferers have reduced muscle mass or are atrophic, repeated intramuscular injections of vitamin B_{12} can be inconvenient, painful and often require doctor's visits. In some cases at least in the early stages, hospitalization is required. As a result, there is a need for a more convenient, less painful and less expensive method of administering vitamin B_{12}, particularly one that would not require hospitalization or repeated physician contacts.

Unfortulately, up to the present time no efficient method of administering B_{12} which will achieve therapeutically useful blood levels of the vitamin except parenteral administration has been devised.

In 1953 and 1954 Monto et al in Am. J. Med. Sci., 223, 113 (1953) and Arch. of Int. Med. 93,219 (1954) described administration of B_{12} by nasal inhalation and instillation. The vehicles for administration were aqueous isotonic sodium chloride solution and lactose powder. Although the results were reported as effective, safe and economical, the fact is that parenteral administration remains the only method regarded by the medical community as a safe, reliable and effective method for treating vitamin B_{12} deficiencies in humans. No composition for nasal inhalation or ilstillation has become comemrcially available for nasal administration to mammals. There have been no published descriptions of compositions for nasal administration of a vitamin B_{12} by aerosol techniques of which applicant is aware.

The difficulty with nasal instillation by nasal dosage as the procedure is described in the cited articles is that most of the B_{12} passes immediately into the throat. It is not in contact with the nasal mucosa for a sufficient period of time to permit useful and uniform absorption. Most of the B_{12} so administered is, in fact wasted.

Aerosol compositions have now been discovered for the nasal administration of B_{12} in contact with the nasal mucosa for an extended period of time. During the time the compositions are in such contact, the B_{12} is uniformly absorbed from the compositions through the nasal mucosa and is then uniformly distributed systemically. The use of the compositions, because of the efficiency with which the B_{12} is absorbed allows the use much lesser amounts of B_{12} then is normally present in parenteral B_{12} compositions. Moreover, since the patient can self administer the B_{12}, the need for hospitalization or physician contacts is minimized and may even be eliminated.

THE INVENTION

This invention provides vitamin B_{12} containing aerosol compositions specifically furmulated for nasal administration which will retain the B_{12} in contact with the nasal mucosa for a sufficiently long period of time to permit consistent, continuous and uniform absorption of therapeutically effective amounts of a vitamin B_{12} through the nasal mucous membrane.

The invention, therefore comprises aerosol compositions containing a therapeutically effective amount of vitamin B_{12}. More specifically it comprises therapeutic compositions in aerosol form for nasal administration. The B_{12} is in an isotonic aqueous buffer and is sealed in a container equipped with a metering valve which when actuated will provide a spray of particles in which the particle size of the droplets of the spray

is from 5 to 50 microns. The invention also comprises the method of using the compositions to treat humans afflicted with a vitamin B_{12} deficiency.

The pH of the compositions of the invention is from about 4 to 6. At this pH, B_{12} is stable so that the compositions have a shelf life which may be a year or more. Additionally, at this pH, irritation of the nasal mucosa is minimal. The pH is maintained with a physiologically acceptable buffer composition suitably an acetate, phosphate, phthalate, borate, or other buffer.

An acetate buffer is preferred for convenience and economy.

The isotonicity of the composition is accomplished using sodium chloride, or other pharmaceutically acceptable agent such as dextrose, boric acid, sodium tartrate or other inorganic or organic solute. Sodium chloride is preferred particularly for buffers containing sodium ions.

The compositions of this invention may contain a humectant to inhibit drying of the mucous membrane and to prevent irritation. Any of a variety of humectants can be employed including, for example sorbitol, propylene glycol or glycerol. The concentration will vary with the selected agent, although the presence or absence of these agents, or their concentration is not an essential feature of the invention.

An enhanced absorption of B_{12} across the mucous membrane may be accomplished employing a surfactant. Typically useful surfactants for these therapeutic compositions include polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides such as Tween 80, Polyoxyl 40 Stearate, Polyoxyethylene 50 Stearate and Octoxynol. The usual concentration is from 1% to 10% based on the total weight.

A preservative may be employed to increase the shelf life of the compositions. Benzyl alcohol is suitable, although a variety of preservatives including, for example, Parabens, thimerosal, chlorobutanol, or benzalkonium chloride may also be employed. A suitable concentration of the preservative will be from 0.02% to 2% based on the total weight, although there may be appreciable variation depending upon the agent selected.

The compositions of the invention are dispensed from a sealed container equipped with ~~a metering~~ valve which when actuated releases a spray in which the particle size of the spray droplets is from about 5 to 50 microns, preferably 10 to 20 microns. It has been found that if the spray droplets are below this range, they go directly through the nasal passages into the lungs. If they are larger, they coalesce into large drops which either run out of the nose or down into the throat.

Suitable containers and metering values are available commercially and need not be described here. They are available for use in packaging systems which deliver the aerosol compositions by all of the conventional aerosol techniques. These include mechanical pumps in which delivery is made by movement of a piston; compressed air mechanisms in which delivery is made by hand pumping air into the container; compressed gas techniques in which delivery is made by the controlled release of a compressed gas in the sealed composition; and liquid propellant techniques in which a low boiling liquid hydrocarbon or halohydrocarbon is vaporized to exert a pressure and force the aerosol composition through the metered valve. All of these systems are useful in the practice of this invention.

The most widely employed compressed gas for delivering aerosol compositions is nitrogen. The principal hydrocarbon is butane, although other low boiling hydrocarbons can be used in pure or mixed form. Fluorocarbons of the Freon series are useful in the invention. These include, for example, Freon 11, 12 and 14 and Fluorocarbon-FC152A.

All of the foregoing systems and propellants are useful for the nasal administration of the aerosol compositions of this invention.

Due to the efficiency with which B_{12} is absorbed from the compositions of this invention, a therapeutically effective amount of B_{12} for nasal administration will normally be appreciably less than for conventional methods of administration. Typically the concentrations of B_{12} in the compositions of this invention will be from about 0.05% to 1% by weight based on the total weight. The concentration may vary considerably however with the selected method of delivery. If the composition is a simple aqueous solution of B_{12}, possibly including excipients in solution or suspension under a compressed gas, the preferred concentration will be within the above range. But if the composition also contains propellants, the concentration of B_{12} might vary. The important point is that the concentration be selected so that, acting together with the selected metering valve, each spray will deliver a dosage unit of from about 50 to 1000 micrograms. It is of course possible to design an equivalent combination of concentration and metering valves so that a dosage unit containing 50 to 1000 micrograms of B_{12} is delivered by two, three or even more valve actuations and resulting sprays.

The following aerosol compositions of this invention are useful for delivery by compressed gas systems or by mechanical pumps.

Benzalkonium Chloride NF	0.020 g
Thimerosal USP	0.002 g
Acetic Acid NF	0.100 g
Sodium Acetate (Anhydrous) USP	0.270 g
Sodium Chloride USP	0.820 g
Cyanocobalamin USP	0.200 g
Water, Purified USP	q.s. 100.000 ml

Phenylmercuric Acetate NF	0.002 g
Acetic Acid NF	0.100 g
Sodium Acetate (Anhydrous) USP	0.270 g
Boric Acid NF	1.740 g
Cyanocobalamin USP	0.500 g
Water, Purified USP	q.s. 100.000 ml

Benzalkonium Chloride NF	0.020 g
Phenylmercuric Acetate NF	0.002 g
Acetic Acid NF	0.100 g
Sodium Acetate (Anhydrous) USP	0.270 g
Boric Acid NF	1.740 g
Cyanocobalamin USP	1.000 g
Water, Purified USP	q.s. 100.000 ml

Other compositions of this invention are produced by dissolving the B_{12} in a solvent which is miscible with the selected propellant and taking the solution up in the propellant. The resulting solution is sealed in an appropriate container having a metered valve. Suitable solvents include, for example, ethylene glycol and polyethylene glycol. When the valve is acuated the B_{12} is expelled in the solution and deposits on the nasal mucosa.

WHAT IS CLAIMED IS

1. A therapeutic composition in aerosol form for nasal administration comprising a therapeutically effective amount of a vitamin B_{12} in an isotonic aqueous buffer at a pH of from about 4 to 6 in an aerosol formulation in a sealed container equipped with a metering valve which when actuated provides a spray of particles in which the particle size is from 5 to 50 microns.

2. A therapeutic composition of Claim 1 wherein the vitamin B_{12} is cyanocobalamin.

3. A composition of Claim 1 wherein the spray particle size is 10 to 20 microns.

4. A therapeutic composition in aerosol form for nasal administration containing a vitamin B_{12} in an isotonic aqueous buffer at a pH of from about 4 to 6 in an aerosol formulation is a sealed container equipped with a metering valve which when actuated provides a spray of particles in which the particle size is from 5 to 50 microns each separate spray containing from 50 to 1000 micrograms of a vitamin B_{12}.

5. A therapeutic composition as in Claim 4 wherein the vitamin B_{12} is cyanocobalamin.

6. A therapeutic composition as in Claim 4 or 5 wherein the spray particle size is 10 to 20 microns.

7. A method of treating a human for a vitamin B_{12} deficiency which comprises nasal administration by aerosol spray to a human in need of such treatment of an aerosol composition containing a therapeutically effective amount of a vitamin B_{12} in an isotonic aqueous buffer at a pH of from about 4 to 6 from a container in

which the composition is sealed, said container equipped with a metering valve which when activated provides a spray of particles in which the particle size is 5 to 50 microns.

8. A method as in Claim 7 wherein the vitamin B_{12} is cyanocobalamin.

9. A method as in Claim 7 or 8 wherein the particle size is 10 to 20 microns.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US86/00665

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A61L 9/04;A61K 31/70;A61M 11/00; B05B 7/30; A61M 37/00

U.S.: 424/45;514/52;128/200.14,200.23; 239/350; 604/140

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	424/45; 514/52; 128/200.14,200.23; 239/350; 604/140

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

CAS-ON-LINE: Vitamin B_{12}/Cyanocobalanine & Aerosol

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	U.S.,A, 2,746,796 (ST. GERMAIN) 22 May 1956, see Figures 1 and 2, column 1, lines 41-43 and 46-57 and claim 2.	1-9
Y	U.S.,A, 2,914,222 (MESHBERG) 24 November 1959, see Figure 7, column 1, lines 45-48 and claim 1.	1-9
Y	U.A.,A. 4,525,341 (DEIHL) 25 June 1985, see column 1. lines 6-9, column 2, lines 1-2 and 9-11 and Example 1 in column 4.	1-9

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
17 June 1986	20 JUN 1986
International Searching Authority [1]	**Signature of Authorized Officer** [20]
ISA/US	DOUGLAS W. ROBINSON

Form PCT/ISA/210 (second sheet) (October 1981)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

X	Chemical Abstracts, Volumn 66, No. 15, issued 10 April, 1967 (Columbus, Ohio, U.S.A), (N.K. SHINTON) "Vitamin B_{12} absorption by inhalation" see page 6024, column 2, the abstract No. 64246e, Brit. J. Haematol. 12(1),75-9(1967)(Eng.)	1-9

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers_____, because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers_____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.